Cilostazol May Suppress Restenosis and New Contralateral Carotid Artery Stenosis After Carotid Endarterectomy

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Abstract

Carotid artery restenosis is a serious complication following carotid endarterectomy (CEA), so preventative management of the risk factors is important. The present study investigated the potential of cilostazol, a mediator of vascular stabilization as well as inhibitor of platelet aggregation, to suppress restenosis on the ipsilateral carotid artery and new plaque development on the contralateral carotid artery. Eighty-two patients treated by CEA were divided into two groups according to the postoperative antiplatelet aggregation drugs into the cilostazol and other groups. Patients were periodically examined for recurrence of the plaque on the ipsilateral side, development of plaque on the contralateral side, and the bilateral intermedia thicknesses measured by ultrasonographic examination for up to 6 years. Restenosis and development of the contralateral plaque were not detected in any patients in the cilostazol group, whereas such changes were found in seven patients in the other group. Cilostazol might be effective to inhibit the growth mechanism of plaque.

Key words: cilostazol, carotid endarterectomy, restenosis

Introduction

Carotid artery stenosis is a surgically curable cause of cerebral stroke induced by an inextricably complicated pathogenesis of thrombosis, hemodynamic compromise based on poor cerebral blood flow, embolism from plaque, and thrombo-embolism. Carotid endarterectomy (CEA) and carotid artery stenting (CAS) for serious carotid artery stenosis were effective preventative treatments for cerebral stroke in major randomized trials.^{6,18,23)} However, recurrence of the carotid plaque was a common postoperative complication.^{1,3,7,8,15,17,20,27,28)} The pathological mechanism of carotid plaque is profoundly related to the inflammation process,^{5,14)} so some agents can be effective.^{2,16,26)}

The present study investigated the preventative effect of cilostazol, which acts as a selective inhibitor of platelet aggregation as well as a stabilizer of the vascular membrane,^{9,11,13,21,30)} against the development of plaque compared with other antiplatelet aggregation drugs (APADs).

Patients and Methods

This study included 82 patients treated for severe stenosis of the cervical carotid artery who were treated by CEA by the same neurosurgeon in our neurosurgical hospital. The surgical indications for CEA were limited to severe carotid artery stenosis (more than 75%) or ulcer formation causing cerebral infarction. Patients were routinely given an APAD after CEA, and classified into two groups by the type of agent: cilostazol or others. Cilostazol was given 200 mg/day postoperatively to 34 patients. Other APADs were given to 48 patients because the agent excluding cilostazol was previously prescribed for other diseases or side effects of cilostazol such as palpitation or headache. The other APADs were aspirin (33 patients), ticlopidine (8 patients), clopidogrel (2 patients), and warfare (5 patients). Patients who received two or more types of APADs or changed APAD during the protocol were excluded from this study.

Patients underwent postoperative ultrasonography several times to monitor for recurrence of plaque on the ipsilateral side, new development of contralateral plaque, and to examine the inter-media

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thickness (IMT) of the bilateral carotid arteries measured at the far wall 10 mm proximal from the carotid bifurcation without plaque. These sequential ultrasonographic changes were evaluated at 1, 3, and 6 months, and every year up to the 6 years at the longest following the surgical procedure. Mean observation periods were 4.2 years in the cilostazol group and 4.0 years in the other group. Patients observed for less than 1 year postoperatively were excluded. Stenosis rate was measured with the ultrasonographic method by the North American Symptomatic Carotid Endarterectomy Trial Collaborators.²³⁾ Restenosis and development of the contralateral plaque was defined as recurrent luminal narrowing of <30%, <50%, <75%, and <100%. IMT was evaluated on the final ultrasonographic image. All ultrasonography examinations were performed by the same technical operator in our hospital. The chi-square test and Fisher's test were used to determine statistical significance at the $p < 0.05$ level.

Results

Table 1 shows the clinical data of the two patient groups. Sex and mean age showed no differences. Risk factors of hypertension, diabetes mellitus, and hyperlipidemia were similar in both groups. Statin type agents were similarly prescribed in the two groups.

Bilateral IMTs were periodically measured postoperatively. Quantitative changes of IMT were -0.04 mm in the cilostazol group and -0.002 mm at the ipsilateral site in the other group, and $+0.01$ mm and $+0.08$ mm, respectively, at the contralateral site (Fig. 1). No significant differences were found on either side.

All patients had no residual plaque at the ipsilateral site immediately after CEA. Recurrence of the plaque was not detected in any of the patients in the cilostazol group. However, two patients in the other group had recurrent plaque postoperatively, luminal narrowing was <30% in one patient and 30–50% in the other. Both patients were asymptomatic and were identified by the periodic echocardiography at 3 and 4 years postoperatively. The restenosis ratios demonstrated significant differences between the two groups on Fisher's test ($p < 0.05$).

All luminal narrowing at the contralateral plaque was 0% or <30% at most immediately after surgery. Postoperative sequential change of the plaque was not detected in any of the patients in the cilostazol group, but plaque development was found in five patients in the other group (<30% in 3 patients, 30–50% in 1, and 75–100% in 1), with statistically

Table 1 Clinical data of the patients

	Cilostazol (n = 34)	Others (n = 48)	Chi-square test
Sex (male:female)	32:2	42:6	NS
Mean age (yrs)	68.7	68.6	NS
Risk factors			
hypertension	22	37	NS
diabetes mellitus	13	17	NS
hyperlipidemia	14	24	NS
Statin medication	8	12	NS

NS: not significant.

Fig. 1 Quantitative comparison of the intermediate thickness on the ipsilateral and the contralateral sides between the cilostazol (open columns) and other groups (closed columns). Values are mean $\pm$ standard error of the mean. NS: not significant.

significant difference ($p < 0.05$). These five patients were asymptomatic and were identified at 2 to 4 years postoperatively.

Six of seven patients with postoperative restenosis or contralateral plaque development had no hyperlipidemia. One patient with contralateral plaque, associated with 90% stenosis finally treated with CEA, had had hyperlipidemia before and was treated with pravastatin.

Discussion

Management of the perioperative complications of CEA such as restenosis must include ultrasonography of the ipsilateral carotid artery for a long follow-up period. Restenosis, defined as more than 50–80% stenosis, occurs with a probability of 5–31% up to 5 years after CEA.^{3,7,8,15,17,20,27,28,31)} The variable definition of restenosis is likely to be the cause of the wide range in probabilities. This study found 2 (2.3%) of 84 patients with any type of stenosis and no patients with >50% restenosis. CAS has a relatively lower incidence of restenosis as a postoperative complication.^{4,10)} However, the re-

nosis rate should not be simply compared to that of CAS because the CAS procedure is just simple dilation of the plaque, which still remains postoperatively, and the mechanism of restenosis at a metal stent is assumed to be different to that after CEA. We also need to consider the efficacy of cilostazol against residual plaque following CAS.

The probability of contralateral carotid artery stenosis is 15.8% over 5 years.⁷⁾ Long-term follow-up study after CEA demonstrated that the risk of contralateral progression was more than twice the risk for the ipsilateral side.⁷⁾ This study found any contralateral stenosis in 5 (6.0%) of the 84 patients. However, no progression of contralateral stenosis was identified in the patients treated postoperatively with cilostazol, suggesting that cilostazol may inhibit progression of carotid plaque.

Inflammation is known to be central in the mechanism of plaque development.^{5,14)} Exposure to risk factors such as diabetes mellitus, hyperlipidemia, hypertension, or smoking may induce activation of the endothelial cells, followed by white blood cell attractant, adhesion molecule expression, and finally active interactions of leukocyte-endothelial cells. Leukocytes and endothelial cells activate each another through adhesion molecules and release various inflammatory cytokines and chemokines. Monocytes migrate into the endothelium through adhesion molecules, then ingest lipids to become foam cells. Accumulation of foam cells and reactive proliferation of the vascular smooth muscles finally result in formation of atherosclerotic plaque. Restenotic plaque in the postoperative periods is mainly distinguished by hyperplasia of the vascular smooth muscle in the acute period, around the postoperative 1st year, but is the same as common plaque pathogenesis in the chronic period around the postoperative 4th to 5th years.^{12,17)}

Postoperative management to suppress plaque regrowth has mainly depended on the strict control of risk factors. In general, APADs have little potential to inhibit plaque development. Cilostazol is a selective inhibitor of phosphodiesterase 3 which increases intracellular cyclic adenosine monophosphate content, resulting in inhibition of platelet aggregation and peripheral vasodilation.^{9,21,30)} Cilostazol effectively suppresses the incidence of cerebral stroke, like other APADs, but also has a unique stabilization effect on the vascular membrane, which suppresses certain inflammation mechanisms.^{11,13)} Various actions of cilostazol may be related to these process as follows: inhibition of vascular smooth muscle proliferation²⁹⁾; suppression of adhesion molecule expression like intercellular adhesion molecule-1 and vascular adhesion molec-

ule-1 on the vascular membrane^{24,25)}; and inhibition of production of various cytokines like platelet-derived growth factor,¹⁹⁾ macrophage chemoattractant protein-1, and tumor necrotic factor-alpha.²²⁾ These effects can suppress inflammation processes and finally prevent progression of atherosclerosis. We previously demonstrated that such anti-inflammatory functions of cilostazol could suppress cerebral vasospasm following subarachnoid hemorrhage.³²⁾

Cilostazol has the potential to prevent the development of carotid plaque in both the acute and chronic postoperative periods. Statins also have similar efficacy against carotid plaque.²⁶⁾ The two groups in this study showed no difference in hyperlipidemia and the patients with the progressive plaque did not have hyperlipidemia excluding the patient medicated with pravastatin. Therefore, the effect of hyperlipidemia and statins could not be clarified in this study. Further study of the interactions between cilostazol and statin will be necessary before the preventative effect of cilostazol against restenosis and new contralateral stenosis can be confirmed.

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Commentary

The authors report significantly less frequent restenosis on the ipsilateral side and progression of stenosis on the contralateral side after carotid endarterectomy in patients receiving cilostazol (N = 34) versus patients receiving other antiplatelet or anticoagulant agents (N = 48). Both groups were concurrent, operated at the same institution, by the same surgeon, and had similar demographic and gross risk factor characteristics, and both were followed for at least one year (mean of about 4 years in both groups) with regularly scheduled standardized carotid Doppler. Remarkably, there were in fact no instances of restenosis or progression of stenosis in the cilostazol group, while the rate of progression was similar to published studies in the control group.

The authors speculate about potential mechanisms of cilostazol effect on plaque progression or restenosis. Cilostazol is a selective inhibitor of phosphodiesterase 3 which increases intracellular cyclic adenosine monophosphate content, resulting in inhibition of platelet aggregation and peripheral vasodilation. Cilostazol has been shown to effectively prevent cerebral ischemic stroke, like other antiplatelet agents, but also has a unique stabilization effect on the vascular membrane, which suppresses certain inflammation mechanisms. Various actions of cilostazol may be related to these processes, including the inhibition of vascular smooth muscle proliferation, suppression of adhesion molecule expression like intercellular adhesion molecule-1 and vascular adhesion molecule-1 on the vascular membrane, and inhibition of production of various cytokines. These effects can suppress inflammation processes and inhibit the progression of atherosclerosis. The authors had previously demonstrated that such anti-inflammatory functions of cilostazol could suppress cerebral vasospasm following subarachnoid hemorrhage.

The results are compelling but we must be cautious about the retrospective nature of the study, its unblinded nature (possibly biasing patient selection or interpretation of restenosis data), and the nonrandomized and necessarily different intention to treat with agent or control. In fact, some patients receiving other agents than cilostazol "had other medical indications for those agents," or did not tolerate cilostazol. Despite grossly similar prevalence of risk factors, the two cohorts may have been inadvertently preselected with different risk factor severity and predisposition to disease progression. And there is no mention of smoking prevalence and severity in the two groups, which may have introduced additional bias.

Finally, only a fraction of cases in both groups received concomitant statins, which would currently

represent a standard of care in such patients, and have been shown to prevent progression of atheromatous plaque. So it is unclear if any benefit of cilostazol would persist in conjunction with current best medical therapy with statins. These questions must be addressed in properly designed prospective randomized double blinded clinical trials.

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Carotid endarterectomy (CEA) is one of the main surgical procedures used for carotid stenosis. Restenosis after CEA remains an unsolved issue, and surgery for recurrent carotid stenosis has higher complication rates than primary CEA. Cilostazol is a unique antiplatelet drug that has vasodilatory effects and inhibits smooth muscle cell proliferation. The authors present a retrospective analysis of 82 postoperative patients following CEA, and showed that cilostazol suppressed restenosis of the ipsilateral carotid artery postoperatively, and plaque development on the contralateral carotid artery, compared to other anti-platelet aggregation drugs (APADs). The control group was treated with various drugs (i.e. aspirin, ticlopidine, clopidogrel, and warfarin) as other APADs in this study, and statin has a similar effect against carotid plaque. Also, the number of patients was limited, so further study is needed.

Carotid artery stenting (CAS) has been advocated as an alternative to CEA in high-risk surgical patients. The recent Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)¹⁾ demonstrated that restenosis is about three times more common after CAS than after CEA, and is associated with recurrent ipsilateral cerebrovascular symptoms. Therefore, the effect of cilostazol against restenosis after CAS is also of interest.

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